

Application No. EP 0594612 of Miettinen, *et al.* (“Miettinen”) and U.S. Pat. No. 5,277,910 of Hidvégi (“Hidvégi”).

The Examiner maintains that Jandacek discloses significant hypocholesterolemic activity associated with phytosterols, and that phytosterols can be used along with saturated and unsaturated fatty acids for reducing serum cholesterol content in a mammal. The Examiner also contends that Hasegawa teaches the use of linoleic acid and/or phytosterol for lowering serum cholesterol in mammals.

The Examiner acknowledges that neither Jandacek, nor Hasegawa, teaches the use of phytosterols and *conjugated* fatty acids for lowering serum cholesterol levels. However, the Examiner contends that Miettinen discloses the use of fatty acid esters of  $\beta$ -sitosterol and  $\beta$ -sitostanol to lower serum cholesterol levels, wherein the fatty acids may be derived from rapeseed oil. The Examiner further contends that, “[i]t is well known that rapeseed oil contains about 90% unsaturated fatty acids having one or more double bonds.” (Paper No. 12, p. 4). The Examiner contends that Hidvégi teaches a pharmaceutical composition containing sitosterol and linoleic acid, in gelatin capsule form, for lowering blood-lipid levels.

On the basis of these contentions, the Examiner argues that it would have been obvious to one of ordinary skill in the art to employ both a phytosterol and a conjugated fatty acid in a method of reducing serum cholesterol levels. The Examiner argues that one of ordinary skill in the art would have found motivation to do so in the cited references because Jandacek allegedly discloses that both phytosterols and unsaturated fatty acids are useful for reducing serum cholesterol. The Examiner argues that the disclosure of unsaturated fatty acids includes conjugated fatty acids. The Examiner further argues that Hasegawa’s teaching of linoleic acid, provides additional motivation.

Applicant strenuously, but respectfully, traverses the Examiner’s rejection and the arguments and contentions set forth in support thereof, for the following reasons.

It is well-settled that in order to establish a *prima facie* case of obviousness, and thus shift the burden of proving non-obviousness onto Applicant, the Examiner must show all of the following three criteria: (1) there must be some suggestion or motivation to modify or combine the references as suggested by the Examiner (it is not sufficient to say that the cited

references can be combined or modified without a teaching in the prior art to suggest the desirability of the modification); (2) there must also be a reasonable expectation of success; and (3) the references as combined must collectively teach or suggest all limitations of the claims. The teaching or suggestion to combine and modify the cited art and the reasonable expectation of success must both be found in the prior art and not in the Applicant's Specification. (M.P.E.P. §2143).

None of the three criteria necessary to establish such a *prima facie* case of obviousness has been satisfied.

Applicant's claimed invention is directed to hypocholesteremic preparations comprising at least one component (a) selected from the group consisting of phytosterols and phytosterol esters *and* at least one component (b) selected from *conjugated* fatty acids having from about 6 to about 24 carbon atoms and glycerides of *conjugated* fatty acids having from about 6 to about 24 carbon atoms; and to methods of reducing serum cholesterol content in a mammal comprising administering such a preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal.

**None of the cited references teaches or suggests the use of a conjugated fatty acid.** Each of the embodiments of Applicant's claimed invention specifies the use or inclusion of a conjugated fatty acid having from about 6 to about 24 carbon atoms and/or glycerides thereof. It is well-known that "conjugated", when referring to chemical bonds, means two or more double bonds with alternating single bonds, for example,  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ .

Jandacek does not teach or suggest the use of a conjugated fatty acid in conjunction with a phytosterol to lower serum cholesterol. Jandacek discloses the use of a steroid solubilizing agent in conjunction with phytosterols for the reduction of cholesterol levels. (*See*, Jandacek, col. 2, lines 1-5). Jandacek specifically notes that a problem confronting the use of phytosterols for reducing cholesterol levels is their low solubility in edible oils. (*See*, Jandacek, col. 1, lines 42-51). Jandacek is directed to increasing the solubility of phytosterols in edible oils. In an effort to increase the solubility of a phytosterol in an edible oil, Jandacek teaches the use of a steroid solubilizing agent which may be selected from "free fatty acids, fatty acids esters and alkanols." (*See*, Jandacek, abstract). Jandacek does not teach the use of fatty

acids *per se* to lower cholesterol levels. In fact, Jandacek does NOT associate any hypocholesterolemic effect with the fatty acids taught therein. Moreover, Jandacek does not teach the use of any polyunsaturated acids, let alone conjugated acids. There is no teaching or suggestion in Jandacek that the solubility of a phytosterol in an edible oil can be increased by the incorporation of a *conjugated* fatty acid, and thus there is no motivation to modify its teachings in such a way.

Hasegawa teaches the use of linoleic acid. Hasegawa does not teach or suggest the use of any conjugated fatty acids. Hasegawa does not recite conjugated linoleic acid as a component in any of the disclosed compositions.

The Examiner has acknowledged that neither Jandacek, nor Hasegawa, teaches conjugated fatty acids. However, the Examiner argues that Miettinen cures this deficiency. Applicant respectfully disagrees. The Examiner argues that because Miettinen teaches the use of rapeseed oil fatty acids, that the use of conjugated fatty acids is obvious. This is incorrect. To begin with, Miettinen is directed to esters of fatty acids and phytosterols, not mixtures of the two. Second, rapeseed oil, which contains polyunsaturated fatty acids, is not known to be a source of *conjugated* fatty acids. Polyunsaturation is not equivalent to conjugation, nor does polyunsaturation automatically suggest conjugation.

Each of the embodiments of Applicant's claimed invention specifies the use or inclusion of a conjugated fatty acid having from about 6 to about 24 carbon atoms and/or glycerides thereof.

None of the cited references teaches or suggests the use of conjugated fatty acids. None of the cited references contains any teaching or suggestion which would motivate one of ordinary skill in the art to modify the teachings of the references to include conjugated fatty acids. Moreover, given the lack of any teaching concerning conjugated fatty acids, one of ordinary skill in the art would have no reasonable expectation of success based upon the cited references.

Applicant submits that none of the cited references, nor a combination thereof, teaches or suggests each and every element of the claimed invention. Specifically, none of the cited references teaches the use of conjugated fatty acids in lowering serum cholesterol levels.

Moreover, none of the cited references teaches the use of a phytostenol compound with a conjugated fatty acid for such a purpose. Miettinen does disclose the use of rapeseed oil. Applicant notes that rapeseed oil does contain a large amount of unsaturated fatty acids. However, the polyunsaturated fatty acids in most rapeseed oils are 9,12 and 9,12,15 isomers of linoleic and linolenic acids, respectively. The disclosure of rapeseed oil does not equate to the disclosure of conjugated fatty acids. With respect to Hidvégi, Applicant notes that linoleic acid is not the same as conjugated linoleic acid, as explained above. Moreover, Hidvégi does not teach the use of sitosterol and linoleic acid. Hidvégi simply notes that the disclosed starting material (*i.e.*, alfalfa) is known to contain some amount of both sterols and fatty acids, which may include linoleic acid (*i.e.*, a non-conjugated acid).

Secondly, Applicant submits that none of the cited references, either alone or in combination, contains a teaching or suggestion which would motivate one of ordinary skill in the art to combine and modify their teachings, as suggested by the Examiner, in order to arrive at the claimed invention. As discussed above, none of the cited references teaches the use of conjugated fatty acids. Absent any specific teaching to use conjugated fatty acids, it cannot reasonably be said that one of ordinary skill in the art would be motivated to modify the references to include their use.

Finally, given the lack of any teaching or suggestion to use conjugated fatty acids in conjunction with phytostenol compounds, and given the lack of any teaching or suggestion motivating such a modification of the prior art, one of ordinary skill in the art would not have a reasonable expectation of successfully achieving Applicant's claimed invention, based upon the cited art.

Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the three criteria necessary to establish a *prima facie* case of obviousness has been satisfied. Thus, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

Lastly, even if it were assumed, for argument's sake, that a *prima facie* case of obviousness could be established based upon the cited references and that such a *prima facie* case of obviousness had been established, which it cannot and has not, any such alleged *prima*

*facie* case of obviousness would be overcome by Applicant's showing of unexpected synergism between the phytosterol(ester)s and the conjugated fatty acids. As evidenced by the Examples set forth in Applicant's Specification, beginning at page 8, line 17, the combination of phytosterol(ester)s and conjugated fatty acids in accordance with Applicant's invention perform better than either component alone in reducing serum cholesterol levels. As can be seen from Table 1, at page 9, the combinations decrease the serum cholesterol levels in amounts greater than either component alone.

In Paper No. 12, the Examiner states that the data shown in Table 1 has been fully considered, but that it is not persuasive. The Examiner criticizes the employment of lauric acid since it is "not even an unsaturated carboxylic acid". (Paper No. 12, p. 10). Applicant would like to respectfully point out that Examples 3 and 4, as set forth in Table 1, utilize a combination of lauric acid esters of phytosterol compounds AND conjugated linoleic acid. Applicant has never asserted that lauric acid is a conjugated fatty acid. However, conjugated linoleic acid certainly is a conjugated fatty acid, as claimed.

Additionally, in Paper No. 12, the Examiner incorrectly alleges that the data fails to show any benefit in utilizing a combination of phytosterol(ester)s and conjugated fatty acids, as opposed to the individual components. In fact, the Examiner alleges that the combinations show less than an additive effect. This is entirely inaccurate. Examples 1, 2, 3, 4 and 5, which combine conjugated linoleic acid and a phytosterol compound, as claimed, show a marked decrease in cholesterol content (as measured by decreased levels of radioactively labeled cholesterol) versus Comparative Examples C1, C2, C3, C4, and C5, which utilize either a phytosterol compound or a conjugated fatty acid alone.

Comparative Example C5 shows that conjugated linoleic acid alone decreases cholesterol content from 98% to 60%. Comparative Example C1, which uses a phytosterol compound by itself, shows a reduction from 93% to 35%. However, Examples 1-5 which combine phytosterols and conjugated linoleic acid show reductions from 93% to 23%, 21%, 22%, 19% and 12%. This evidences synergism between the components and a significant improvement over either component alone.

It is submitted that Applicant's showing sufficiently rebuts any alleged *prima facie* case of obviousness. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the remarks set forth above, Applicant submit that all pending claims patentably distinguish over the prior art of record and known to Applicant, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejections and a Notice of Allowance are respectfully requested.

Respectfully submitted,

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